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Gold-catalyzed diastereoselective domino dearomatization/*ipso*-cyclization/*aza*-Michael sequence: A facile access to diverse fused azaspiro tetracyclic scaffolds†

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A facile and diversity-oriented access to complex tetracyclic benzo[*e*]pyrrolo[2,3-*c*]indole-2,4,7(5*H*)-triones through a post-Ugi gold(I)-catalyzed domino dearomatization/*ipso*-cyclization/*aza*-Michael sequence is elaborated. This process furnishes tetracyclic scaffolds in good yields from readily available precursors with unique diastereoselectivity.

Synthetic chemists are always actuated to explore efficient strategies for the rapid construction of diverse and complex polycyclic molecular architectures resembling biologically active natural products and pharmaceuticals.[1] In this light, during the last two decades homogeneous gold catalysis has served as a powerful tool for the construction of natural products and complex molecules due to the unique characteristic of gold for π-activation of multiple bonds .[2,3] Moreover, the combination of multicomponent reactions[4] (MCRs) and gold-catalyzed post-transformations[5] affords an enormous capability to generate molecular complexity and diversity in a minimal number of steps.

Fused azaspiro tetracyclic N-heterocycles are prominent molecular motifs that are widely present in different alkaloids as (+)-plicamine,[6] (+)-tazettine[7] and (+)-erysotramidine[8] (Fig. 1), which display distinct bioactivities like anticholinergic, immunosuppressive, antitumor, anticancer, and analgesic properties.[9] However, the syntheses of these tetracyclic alkaloids are restricted by multistep procedures and the need of highly functionalized precursors. Moreover, the generation of quaternary carbon centres and the control of the regio- and stereo-chemistry has been a challenging task for organic chemists.[10] Thus, the development of concise, cost-effective, stereoselective and diversity-orientated synthetic strategies to generate structurally diverse complex tetracyclic skeletons is greatly desired.

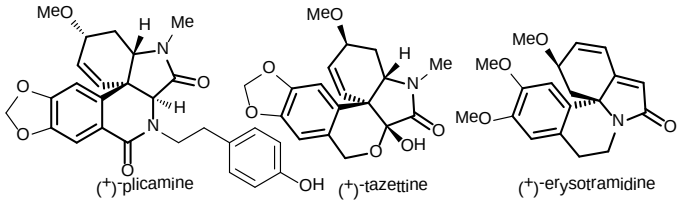
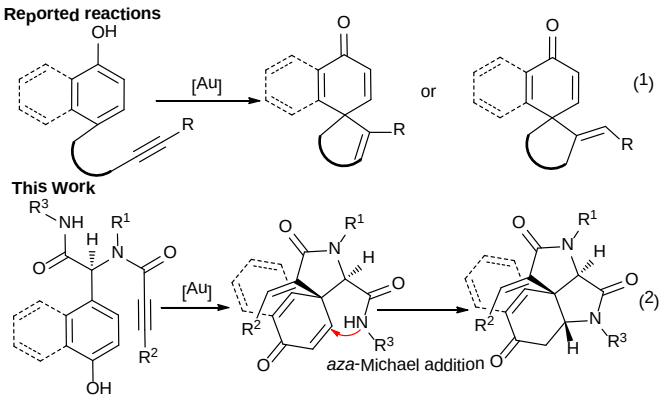


Fig. 1 Representative bioactive fused azaspiro tetracyclic alkaloids.



Scheme 1 Gold-catalyzed cyclization for fused azaspiro tetracycles.

Recently, gold-catalyzed dearomatization/*ipso*-cyclization of phenols attracted a lot of attention due to its unique capacity to generate highly functionalized spirocarbocycles (Scheme 1, eq 1).[11] However, very few reports are dealing with domino strategies to achieve higher levels of the structural complexity by subsequent cyclization of the newly formed unsaturated ketone intermediate after the initial dearomatization/*ipso*-cyclization.[12] Inspired by these results and due to our continuous interest in the development of transition-metal catalyzed post-Ugi domino processes[13] to produce biologically complex heterocycles from readily

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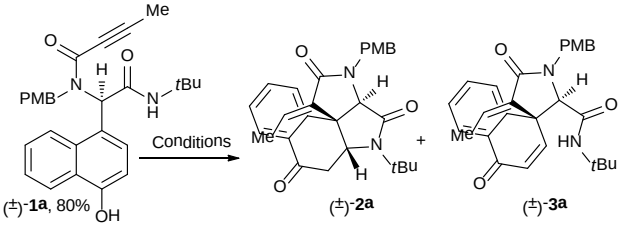
available starting materials, we envisioned that a gold(I)-catalyzed post-Ugi domino dearomatization/*ipso*-cyclization/*aza*-Michael sequence should be highly appealing to construct diverse and complex fused azaspiro tetracyclic scaffolds in only two operational steps (Scheme 1, eq 2).

The easily accessible *N*-(2-(*tert*-butylamino)-1-(4-hydroxynaphthalen-1-yl)-2-oxoethyl)-*N*-(4-methoxybenzyl)but-2-ynamide (**1a**) was obtained *via* Ugi-four component reaction (Ugi-4CR)[14] of 4-hydroxy-1-naphthaldehyde, 4-methoxybenzylamine, *tert*-butyl isocyanide, and 2-butynoic acid with an isolated yield of 80%, and used to test the feasibility of our domino process (Table 1). The initial reaction of **1a** with 10 mol% of $Au(PPh_3)OTf$ in $CDCl_3$ at r.t. gave the spirocarbocyclic product **3a** in 55% isolated yield in 12 h with complete conversion (entry 1). To our delight, a simple increase of the reaction temperature to 70°C, diastereoselectively delivered the desired fused azaspiro tetracyclic scaffold **2a** in 54% yield, along with 13% of the spirocarbocyclic intermediate **3a** in 12 h (entry 2). The isolated yield of tetracyclic alkaloid **2a** was improved to 80% with nearly no intermediate **3a** by doubling the reaction time (entry3). Employing chloride scavengers like $AgBF_4$, $AgSbF_6$ or AgOMs to generate cationic gold resulted in mixtures of

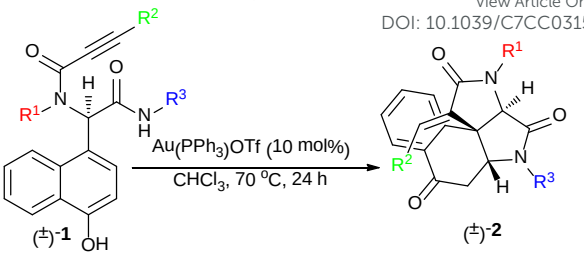
Table 1 Optimization of the domino cyclization.[a]

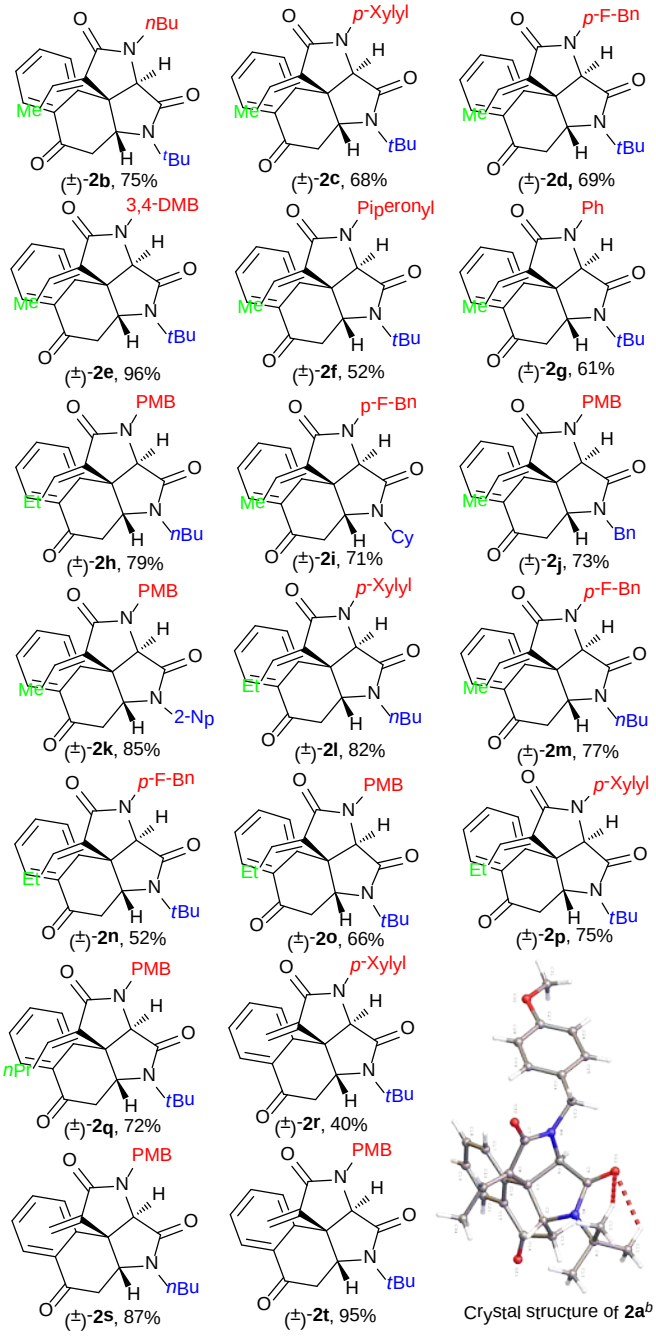


Entry	Catalysts	Solvent	T/ °C	Time /h	Yield[b] of (±)-**2a**/(±)**3a**/%
1	$Au(PPh_3)Cl/AgOTf$	$CDCl_3$	r.t.	12	0/55[c]
2	$Au(PPh_3)Cl/AgOTf$	$CDCl_3$	70	12	54[c]/13[c]
3	**$Au(PPh_3)Cl/AgOTf$**	**$CDCl_3$**	**70**	**24**	**92(80[c])/2**
4	$Au(PPh_3)Cl/AgBF_4$	$CDCl_3$	70	24	51/47
5	$Au(PPh_3)Cl/AgSbF_6$	$CDCl_3$	70	24	41/50
6	$Au(PPh_3)Cl/AgOMs$	$CDCl_3$	70	24	27/63
7	$Au(PPh_3)Cl/AgNTf_2$	$CDCl_3$	70	24	0/93
8	Au(X-Phos)Cl/AgOTf	$CDCl_3$	70	24	86(65[c])/4
9	IPrAuCl/AgOTf	$CDCl_3$	70	24	18/53
10	$Au(PPh_3)Cl$	$CDCl_3$	70	24	0/12
11	AgOTf	$CDCl_3$	70	24	0/0
12	HOTf	$CDCl_3$	70	24	0/0
13	$Au(PPh_3)Cl/AgOTf$	MeCN	70	24	0/12
14	$Au(PPh_3)Cl/AgOTf$	Toluene	70	24	64/0
14	$Au(PPh_3)Cl/AgOTf$	THF	70	24	46/53
16	$Au(PPh_3)Cl/AgOTf$	MeOH	70	24	0/0
17[d]	$Au(PPh_3)Cl/AgOTf$	$CDCl_3$	70	24	67/27

[a] Unless otherwise stated, all reactions were run with **1a** (0.05 mmol) and a catalyst loading of 10 mol% in a screw-cap vial with solvent (1 mL).The catalyst was prepared by mixing the gold catalyst (10 mol%) and silver catalyst (10 mol%) in situ. [b] Yields based on ^1H NMR analysis using 2,4,6-trimethoxybenzaldehyde as internal standard. [c] Isolated yields. [d] Catalyst loading of 5 mol%. PMB = *p*-methoxybenzyl, OMs = methanesulfonate, Tf = trifluoromethanesulfonyl, X-Phos = 2-dicyclohexylphosph-ino-2',4',6'-triisopropylbiphenyl.

Table 2 Scope of the domino sequence.[a]

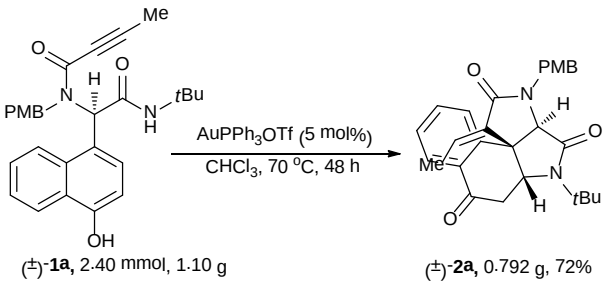




[a] All reactions were run with 1 (0.20 mmol) and $Au(PPh_3)OTf$ (10 mol%) in a screw-cap vial with $CHCl_3$ (2 mL). $Au(PPh_3)OTf$ was prepared by mixing $Au(PPh_3)Cl$ (10 mol%) and AgOTf (10 mol%) in situ; all yields are isolated yields. [b] Crystal structure of **2a** with thermal ellipsoids set at the 50% probability level. Np = naphthyl; PMB = *p*-methoxybenzyl; 3,4-DMB = 3,4-dimethoxybenzyl.

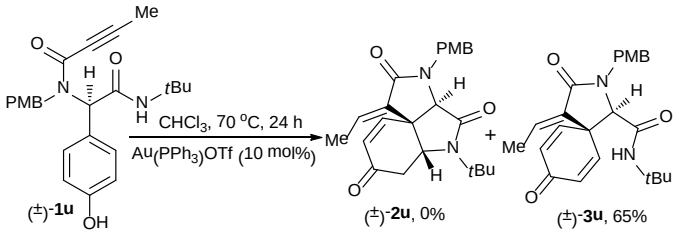
tetracyclic scaffold **2a** and intermediate **3a** (entries 4-6). In case of $AgNTf_2$, solely intermediate **3a** was observed in 93% yield (entry 7). The application of Au(X-Phos)OTf or IPrAuOTf did not improve the yield (entries 8 and 9). Employing solely $AuPPh_3Cl$, AgOTf or HOTf resulted in almost no conversion (entries 10-12). Screening of varies solvents such as MeCN, toluene, THF and MeOH led to chloroform being identified as the best (entries 3 and 13-16). A lower catalyst loading of 5 mol% resulted in the generation of 67% of the desired tetracycles **2a** and 27% of intermediate **3a** (entry 17).

Next, to evaluate the scope and limitations of our optimized conditions, different Ugi adducts were synthesized from 4-hydroxy-1-naphthaldehyde and subjected to the domino cyclization reaction under the optimized conditions (Table 1, entry 3). As illustrated in Table 2, most of the substituents related to the alkyne, the isonitrile, and the amine are well tolerated, delivering the tetracyclic alkaloids in good to excellent yields. The steric effect of the isonitrile moiety did not significantly affect the reaction efficiency (Table 2, **2a**-**g**, **n**-**r**). In case of the Ugi adducts containing a terminal alkyne, exclusive formation of the *exo*-dig products was observed in moderate to good yields (Table 2, **2r**-**t**). The compounds were fully characterized by spectroscopy and the structure of compound **2a** was unambiguously confirmed by X-ray crystallography (Table 2).[15] Moreover, to check the practicality of this approach, a gram-scale reaction was performed. Only 5 mol% of $AuPPh_3OTf$ was employed to accomplish the domino cyclization in 48 h affording the tetracyclic alkaloid **2a** in 72 % yield (Scheme 2).



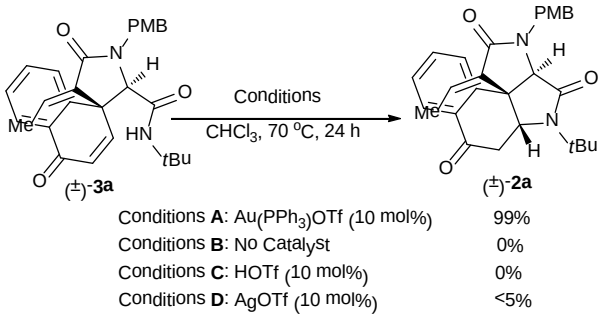
Scheme 2 Gram-scale reaction.

In order to extend our approach for the preparation of fused azaspiro tricyclic scaffolds, the simple phenolic Ugi adduct **1u** was furnished by the Ugi-4CR of 4-hydroxybenzaldehyde with *p*-methoxybenzylamine, 2-butynoic acid, and *tert*-butyl isonitrile, and reacted under the standard conditions. Unfortunately, only the spirocarbocyclic product **3u** was obtained in 65% yield (Scheme 3).



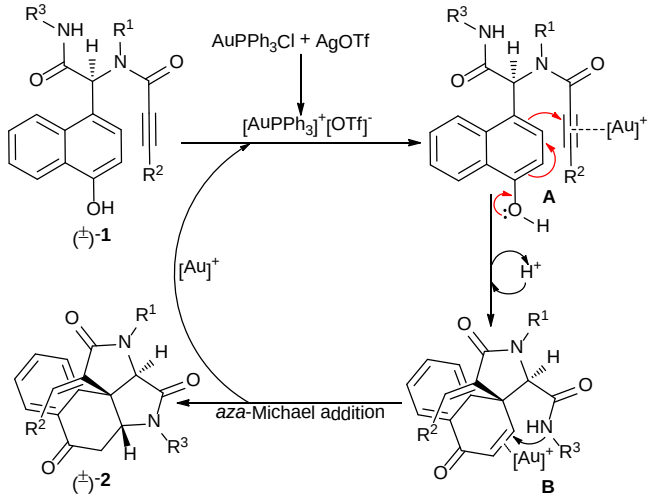
Scheme 3 Attempted synthesis of fused azaspiro tricyclic scaffold.

To further shed light on the reaction mechanism, we investigated the reaction of the spirocarbocyclic intermediate **3a** (Scheme 4). Employment of the optimized conditions delivered the desired fused azaspiro tetracyclic alkaloid **2a** in 99% yield. This result suggests that spirocarbocyclic product **3a** is an intermediate of the domino cyclization. In contrast, no conversion was observed at 70 °C after 24 h in the absence of cationic gold catalysts or if HOTf (10 mol%) was used. Traces of tetracycles **2a** were detected in case of AgOTf (10 mol%). Thus, it was ascertained that dearomatization/*ipso*-cyclization to form **3a,** and subsequent *aza*-Michael addition to generate tetracyclic **2a** are both catalyzed by cationic gold species.[11,16]



Scheme 4 Reaction of the spirocarbocyclic intermediate **3a**.

Based on these observations and previous reports,[3,11] a postulated reaction mechanism for this gold(I)-catalyzed domino dearomatization/*ipso*-cyclization/*aza*-Michael sequence is depicted in Scheme 5. First, the triple bond of Ugi adduct (±)-**1** is π-activated by *in situ* formation of a cationic gold(I) species, followed by nucleophilic attack at the C-4 position of 1-naphthol in a 5-*exo*-dig fashion, resulting in the formation of the spirocarbocyclic intermediate **B**.[11d] Subsequently, *aza*-Michael addition facilitated by π-activation of the cationic gold species, generates tetracyclic scaffold (±)-**2**.



Scheme 5 Proposed mechanism for the gold-catalyzed diastereoselective domino cyclization.

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In summary, we have successfully explored an efficient diversity-oriented post-Ugi gold-catalyzed domino dearomatization/*ipso*-cyclization/*aza*-Michael sequence for the synthesis of functionalized tetracyclic scaffolds from readily available starting materials. The first step, an Ugi-4CR, generates diversity while the second step, a gold-catalyzed domino process generates two rings, one quaternary carbon centre and two stereogenic centers, providing good yields as well as full diastereoselectivity.

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15 CCDC 1515145 (**2a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www. ccdc.cam.ac.uk/data_request/cif.

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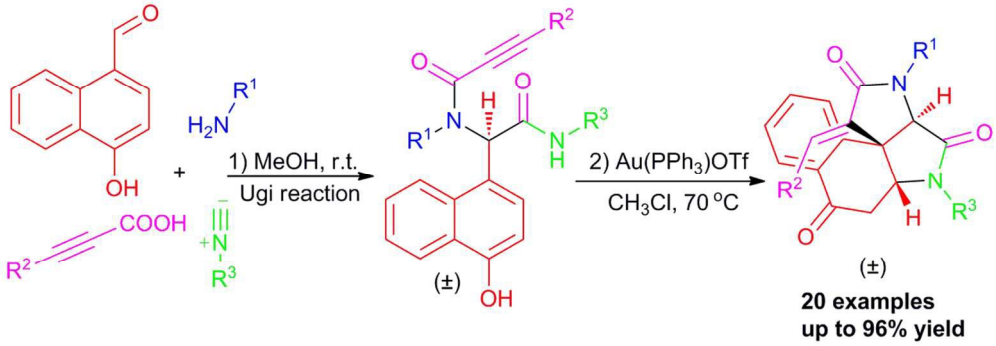

Graphic abstract

108x38mm (300 x 300 DPI)